Economic Analysis of the Use of Drug-Eluting Stents in the Perspective of the Belgian Health Care Sector

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Background: Recent evidence shows that drug-eluting stent devices (DES) substantially reduce the risk of in-stent restenosis compared with classic bare metal stent devices (BMS). In Belgium, the use of BMS is however still standard procedure due to the higher prices of the newer DES.

Research Question: Although the use of DES is more expensive in the short term it might be beneficial in the long term due to the avoidance of patient revascularisation costs. The primary objective of the performed study is to compare the net cost of DES and BMS from the perspective of the Belgian health care sector.

Methods and Results: Cost differences between DES and BMS are driven by the difference in stent price and the difference in the rate of re-intervention. The cost of revascularisation of patients with in-stent restenosis was estimated based on data gathered at the University Hospital of Antwerp (UZA). Data on effectiveness were obtained from a literature review. Due to some important study limitations, an extensive sensitivity analysis was included in this study. In general, the use of DES was cost saving compared to BMS, with savings amounting to € 165 per patient undergoing a PCI with stent implantation in the case of Cypher stent devices and €128 in the case of Taxus stent devices in the base case scenario. For patients with a high risk of restenosis net savings remain in almost all sensitivity analyses.

Conclusion: The use of DES in patients with a high in-stent restenosis risk is cost saving. Price evolutions in the stent device market predict that the use of DES, if not cost saving yet, will in the near future become cost saving for all types of patients.

Key words: drug-eluting - stents - economic analysis – Belgium – restenosis

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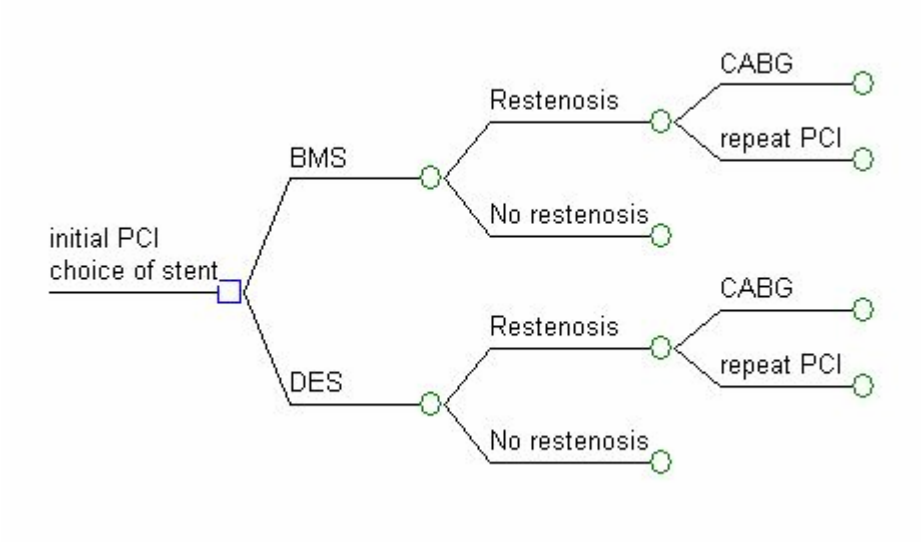
INTRODUCTION

Coronary heart disease is a major cause of death and morbidity in developed countries. It is caused by narrowing of the coronary arteries and is treated by coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI) which include balloon angioplasty and stenting. A common consequence of PCI is restenosis, a re-narrowing of the blood vessel that has been opened by a vascular procedure. When restenosis occurs, the vessel has to be re-opened by PCI or CABG.[1]

The occurrence of restenosis diminishes substantially when coronary stents are used instead of the conventional balloon angioplasty. With balloon angioplasty the vessel is opened by inflation of a balloon that is removed afterwards. With stenting an artificial support device is placed in the vessel after inflation of the balloon to keep the vessel open. Although coronary stents greatly reduce the risk of restenosis, there is still some risk that the stented artery may close; especially for particularly high-risk groups such as diabetics, patients with small arteries, long lesions, etc.[1,2] The possible treatment pathway after a primary PCI intervention with a BMS is represented in the upper branch of the decision tree in figure 1.

Over the past decade the PCI technique to treat coronary artery disease has developed rapidly. Thanks to technical and pharmacological innovations the effectiveness and safety of coronary stent devices has gradually improved. The latest generation coronary stents are the so-called drug-eluting stents (DES), stents coated with pharmaceutical agents suppressing restenosis.[3,4] The possible treatment pathway after a primary PCI intervention with a DES is represented in the lower branch of the decision tree in figure 1. As you can see, the structure of the two branches is identical. But the event rates are different. Evidence shows that rates of in-stent restenosis are lower with DES than with classic bare metal stents (BMS), and the cost of the primary PCI is different because of the higher purchase price of the DES compared with the BMS. Because of this higher purchase price, the use of BMS is still standard procedure in most European countries. In comparison to DES however, patients receiving BMS have higher costs related to revascularization. The question arising here is whether the use of DES might turn out beneficial in the long term, although it is more expensive in the short term.

Figure 1: The treatment pathway after primary PCI in coronary heart disease



RESEARCH QUESTION

The primary objective of the performed study is to compare the net cost (or benefit) of DES and BMS as initial PCI choice from the perspective of the Belgian health care sector (public and private payer). The study assumes that the choice of stent device type has no immediate, but only long term effects on the health condition of the patients. We addressed this question on the basis of a model (see figure 1), for the population as a whole and for some patient subgroups with a higher or lower risk of in-stent restenosis.

METHODS

This study has been split into two main parts. In the first part the difference in effectiveness between drug-eluting and bare metal stent systems was estimated. Data on effectiveness are obtained from literature. In all consulted clinical trials, effectiveness was determined as the percentage of patients not undergoing one or more revascularization procedures. Therefore this measurement method was adopted and it is assumed that there are, apart from the number of follow-up revascularization procedures, no other differences in effectiveness. In the second part the average cost of a revascularization procedure was estimated. Cost data were collected at the University Hospital of Antwerp (UZA). Using the data gathered from the effectiveness and cost study the net cost of BMS was then calculated and compared to the net cost of DES.

EFFECTIVENESS STUDY

Clinical trial selection

Many different stent systems exist and many trials have investigated the effectiveness of these stents. After a profound analysis of the completed trials, focusing on both quantitative and qualitative aspects[i], it was decided to include four stent systems in this study: the CYPHER™ Bx VELOCITY™ bare metal stent system, the CYPHER™ Bx VELOCITY™ drug-eluting stent system, the TAXUS™ Express™ bare metal stent system and the TAXUS™ Express™ drug-eluting stent system. We use effectiveness data on these stents from two trials: the SIRIUS trial and the TAXUS IV trial.

Clinical Endpoints

In this study, the the effectiveness of the stent systems was measured as the relative number of patients undergoing at least one clinically driven target lesion revascularization[ii] within one year after the implementation of the stent device.

[i] The main quantitative and qualitative aspects of the trial analysis are: dimension of the trial sample, period of patient follow-up, double-blindness and randomization of the study, inclusion of subgroups and effectiveness measurement endpoints.

[ii] Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI)

COST STUDY

The difference in total expected costs of bare metal versus drug-eluting stents is calculated. It consists of the difference in cost of the primary intervention and of the follow-up costs.

Incremental cost of the use of drug-eluting stents in the primary intervention

As a whole, the PCI procedure for both the implantation of bare metal and drug-eluting stents is identical, the cost difference between the implantation of the two types of stents is limited to the cost difference of the stent device.

Follow-up costs: Procedure cost of in-stent restenosis treatment and Average treatment cost of patients with in-stent restenosis

Using the PTCA-database of the UZA, we performed the estimation of the average treatment cost of patients undergoing one or more revascularization procedures after the primary intervention. The clinical trial data distinguished between patients undergoing a new PCI-procedure and patients undergoing a CABG-intervention. Since both types of revascularization were expected to differ in cost, separate average costs for both types of treatment were calculated. We selected 44 consecutive patients undergoing a new PCI caused by in-stent restenosis in the stented lesion and 35 consecutive patients undergoing a CABG caused by in-stent restenosis in the stented lesion. Only patients undergoing one or more revascularization procedures at the primary stented lesion after the initial stenting procedure are included. Whenever there was doubt about the direct causal relation between the in-stent restenosis and the revascularization procedure, patients were excluded. After selecting he patients from the PTCA-database the hospital bills of these revascularization interventions were analyzed. All in-hospital costs of the revascularization intervention and hospital care are included. The major components of hospital bills are the procedure cost itself, per diem rate, lump sums, doctor fees and medications.

To estimate the average revascularization cost per patient undergoing a revascularization procedure the data concerning the average cost of a CABG- and PCI-intervention were combined with the proportional incidence of these CABG- and PCI-interventions. Another

factor that was taken into account was the number of repeated revascularizations since the treatment of a patient with in-stent restenosis could include more than one revascularization procedure. As the relative proportion of PCI and CABG is different for each type of stent device, we estimated the average revascularization cost per patient undergoing a revascularization procedure for all four stent devices included in this study.

INCREMENTAL FOLLOW-UP COST OF THE USE OF DRUG-ELUTING STENTS

Based on the data of the effectiveness study, the relative number of patients undergoing at least one clinically driven target lesion revascularization in the first year after the initial intervention for a specific type of stent device was obtained. Multiplying these numbers for the respective stent devices with the average revascularization cost for the respective device from the cost study gives the expected follow up costs. Comparing the expected follow-up costs for patients receiving the bare metal variant and patients receiving the drug-eluting variant of a stent device type gives the incremental follow-up costs (or cost savings) of DES.

NET INCREMENTAL COST OF THE USE OF DRUG-ELUTING STENTS

The last step is to calculate the net costs (or savings) of the use of DES by adding up the extra initial cost generated by the use of DES with the incremental follow up costs (or savings).
The analysis is not only performed for the patient population in general, a distinction is also made between patient types. Therefore some specific subgroups were included defined by diabetic status, vessel diameter and lesion length.

After having analyzed the base case scenario some sensitivity analyses were performed in order to measure the impact of some important limitations and uncertainties in the study results. The variables that were examined in these sensitivity analyses were device effectiveness, price of the coronary stent systems and cost of revascularization.

RESULTS

EFFECTIVENESS STUDY

In this study, the effectiveness of the respective stents was measured by the percentage of patients undergoing at least one clinical driven target lesion revascularization (TLR) within one year after the primary stent implantation. As can be derived from Table 1, drug-eluting stents are more effective than bare metal stents. The gain in effectiveness of the CYPHER™ sirolimus-eluting Bx Velocity™ compared with the bare metal control stent in the SIRIUS-trial is 15.1 percentage points. The gain in effectiveness from the TAXUS™ Express™ Paclitaxel-Elunting Stent compared with the bare metal control stent in the TAXUS IV-study is 10.7 percentage points. As could be expected, the gain in effectiveness is higher for the high-risk patient subgroups. The SIRIUS-trial reports an effectiveness gain of 18 percentage points for the use of CYPHER™ sirolimus-eluting Bx Velocity™ in diabetic patients, 15.9 percentage points in patients with long lesions and 15.7 percentage points in the case of patients with small coronary arteries. The TAXUS-study reports an effectiveness gain of 13.3 and 13.7 percentage points for the respective patient subgroups ‘diabetes type I’ and ‘diabetes type II’ while using the TAXUS™ Express™ Paclitaxel-Eluting Stent. Patients with long lesions have an average gain in effectiveness of 16.6 percentage points with a TAXUS™ Express™ Paclitaxel-Eluting Stent and patients with small coronary arteries a gain in effectiveness of 15.0 percentage points.

Table 1: Percentage of patients undergoing at least one clinical driven target lesion revascularization within one year for drug-eluting and bare metal stents.[5, 6, 7, 8, 9,10, 11,12]

	CYPHER		**Effectiveness difference**	**TAXUS**		**Effectiveness difference**
	DES	BMS	BMS-DES	DES	BMS	BMS-DES
GENERAL POPULATION						
TLR	4.9 %	20 %	**+ 15.1**	4.4 %	15.1 %	**+ 10.7**
TLR-PCI	4.3 %	19.2 %	**+ 14.9**	3.7 %	12.2 %	**+ 8.5**
TLR-CABG	0.9 %	1.7 %	**+ 0.8**	0.8 %	3.7 %	**+ 2.9**
SUBGROUPS						
Diabetics	8.4 %	26.4 %	**+ 18.0**			
Type I				6.2 %	19.4 %	**+ 13.2**
Type II				7.9 %	21.6 %	**+ 13.7**
Non-diabetics	3.7 %	17.6 %	**+ 13.9**	3.5 %	13.2 %	**+ 9.7**
Long lesions	6.0 %	21.9 %	**+ 15.9**	5.5 %	22.1 %	**+ 16.6**
Average lesions				4.4 %	14.1 %	**+ 9.7**
Short lesions	4.0 %	18.6 %	**+ 14.6**	4.1 %	13.4 %	**+ 9.3**
Small coronary arteries	6.6	22.3 %	**+ 15.7**	5.6 %	20.6 %	**+ 15.0**
Average coronary arteries				4.3 %	13.3 %	**+ 9**
Wide coronary arteries	3.1	18.1 %	**+ 15.0**	3.5 %	11.1 %	**+ 7.6**

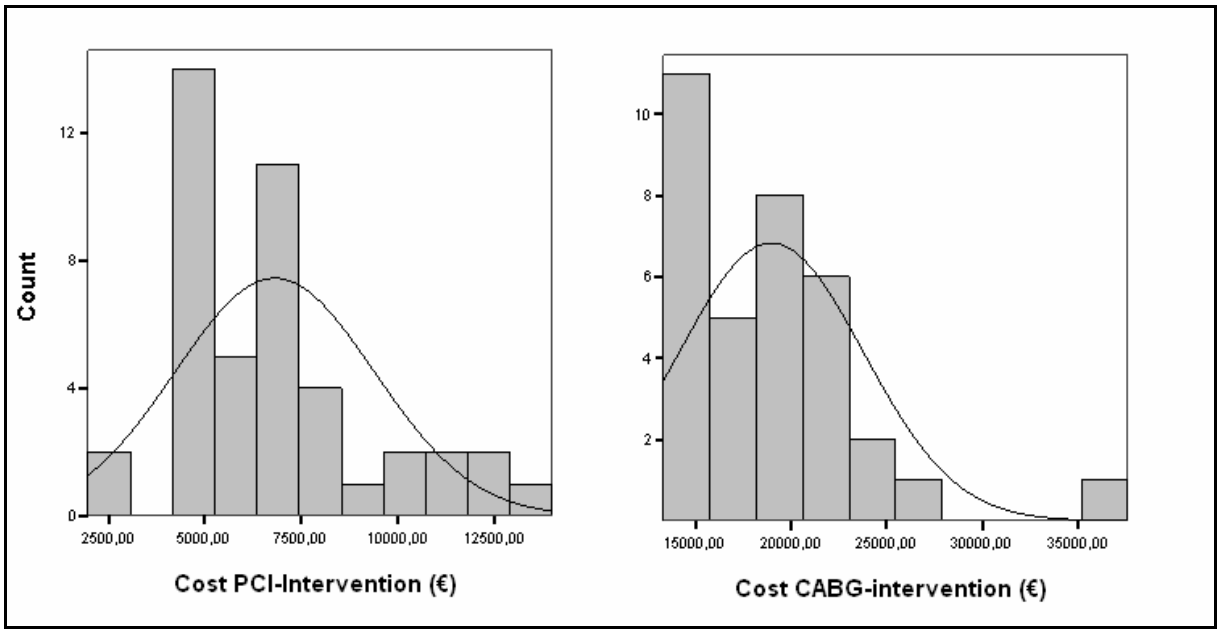
COST STUDY

The incremental cost of a drug-eluting stent in this study is set at €1,000. This is the tariff of the Health Insurance System (HIS) for the extra cost for the use of drug-eluting stents.

The cost of a revascularization procedure caused by in-stent restenosis at the UZA has been estimated as ranging between € 1,977 and € 13,983 with an average of € 6,803[iii]. The cost of a CABG-intervention due to in-stent restenosis has been estimated as ranging between € 13,352 and € 37,572 with an average of € 18,972[iv]

[iii] Standard deviation: € 2,576 and median: € 6,466
[iv] Standard deviation: € 4,811 and median € 18,849

Figure 2: Cost of a PCI- and a CABG-intervention in the University Hospital of Antwerp.



The average revascularization cost per patient undergoing a revascularization ranges from € 8,143.21 for patients initially receiving a Cypher BMS device to € 10,145.00 for patients initially receiving a TAXUS BMS. The estimated average revascularization cost per patient for the Cypher drug-eluting and the TAXUS drug-eluting stent systems is respectively € 9,454.38 and € 9,169.91 (Table 2).

Table 2: Average treatment cost of patients with in-stent restenosis

	Cypher		**TAXUS**	
	DES	BMS	DES	BMS
Average Cost	**€ 9,454.38**	**€ 8,143.21**	**€ 9,169.91**	**€ 10,145.00**

BASE CASE SCENARIO ANALYSIS

Using drug-eluting stents instead of bare metal stents would cause an extra initial cost of € 1000 per patient. On the other hand revascularization costs are reduced due to a lower in-stent restenosis rate.

From the effectiveness analysis it can be concluded that the use of Cypher DES instead of Cypher BMS reduces the need for revascularization with 15.1 percentage point. Regarding the average cost of a revascularization of € 8,143.21 for patients who initially received a Cypher BMS and € 9,454.38 for patients who initially received a Cypher DES the average expected revascularization cost of patients receiving a Cypher BMS was estimated as € 1,628.64. The average expected revascularization cost of patients originally receiving a DES has been estimated as € 463.27. The expected reduction in the revascularization cost by using Cypher DES instead of Cypher BMS is thus € 1,165.37. To estimate the net cost savings of the use of DES the expected cost reduction was weighted with the extra cost for the use of DES. As the cost reduction is estimated as € 1,165.37 and the extra cost as € 1000 this implies that the use of DES would generate cost savings of € 165.37 per patient undergoing a PCI with stent implantation. In the Belgian UZA context, from a societal point of view and for the general population, the use of Cypher DES would thus be cost saving compared with the use of Cypher BMS. This calculation has also been performed for the TAXUS stent system as well as for some predefined high- and low-risk subgroups, results are shown in Table 3. [v]

Table 3: Estimated net cost savings of the use of DES instead of BMS.

	Cypher DES	**TAXUS DES**
GENERAL POPULATION	€ 165.37	€ 128.48
SUBGROUPS		
Diabetics	€ 355.64	
Type I		€ 399.60
Type II		€ 466.90
Non-diabetics	€ 83.39	€ 18.19
Long lesions	€ 216.10	€ 737.70
Short lesions	€ 136.46	- € 16.55
Small coronary arteries	€ 191.95	€ 576.35
Wide coronary arteries	€ 180.83	€ 28.34

[v] detailed calculations can be found in appendix 1

Under the assumptions of the base case scenario, the use of DES seems to be cost saving for the general patient population. The use of DES instead of BMS will, based on these estimations, result in expected net cost savings of € 165.37 per patient in the case of Cypher stent devices and € 128.48 per patient in the case of TAXUS stent devices.
As could have been expected, the net cost savings for the high-risk subgroups are significantly higher than the net cost savings for the low-risk subgroups. The expected net cost savings for the use of DES by diabetics are considerable for both the Cypher DES (€ 355.64) and the TAXUS DES (€ 399.60 / € 466.90). The expected cost savings of the use of DES by non-diabetic patients, estimated as € 83.39 using the Cypher stent system and € 18.19 in the case of the TAXUS stent system do not seem to be significant.

It can also be concluded that the use of TAXUS DES in the case of patients with long lesions is cost saving (net cost savings = € 737.70). On the other hand, the use of TAXUS DES by patients with short lesions does not seem to be cost saving, the extra cost has been estimated as € 16.55. The cost savings for patients with "longer" lesions receiving Cypher DES instead of Cypher BMS were estimated as € 216.10 compared with cost savings of € 136.46 by patients with "shorter" lesions. However, the conservative definitions used in the SIRIUS-trial do not allow us to formulate a final conclusion concerning the short and long lesion patient subgroups receiving Cypher stent devices[vi].

The use of DES in the case of patients with small coronary vessels has also been estimated as cost saving. The calculated net cost savings for the use of the TAXUS DES are estimated at € 576.35; for the use of Cypher DES at € 191.95. For patients with large coronary vessels the estimated cost savings are € 28.34 and € 180.83, respectively for the TAXUS and Cypher stent systems.

Although these study results seem to suggest that the use of DES instead of BMS would be cost saving, some limitations and uncertainties mentioned further in this article preclude a

[vi] In the SIRIUS-trial patients with lesions shorter than the population average of 13.5mm are included in the subgroup 'short lesions', patients with lesions exceeding 13.5mm in the subgroup 'long lesions'. In the TAXUS IV-study patients were included in the subgroups 'short lesions' and 'long lesions' if their lesion were respectively shorter than 10mm and longer than 20mm. In the case of the TAXUS IV-study, the subgroups can indeed be defined as 'short lesions' and 'long lesions'. In the case of the SIRIUS-study, the definitions 'shorter lesions' and 'longer lesions' would be more appropriate.

final conclusion. In order to analyze the impact of these important limitations and uncertainties on the study results some sensitivity analyses were performed.

SENSITIVITY ANALYSES

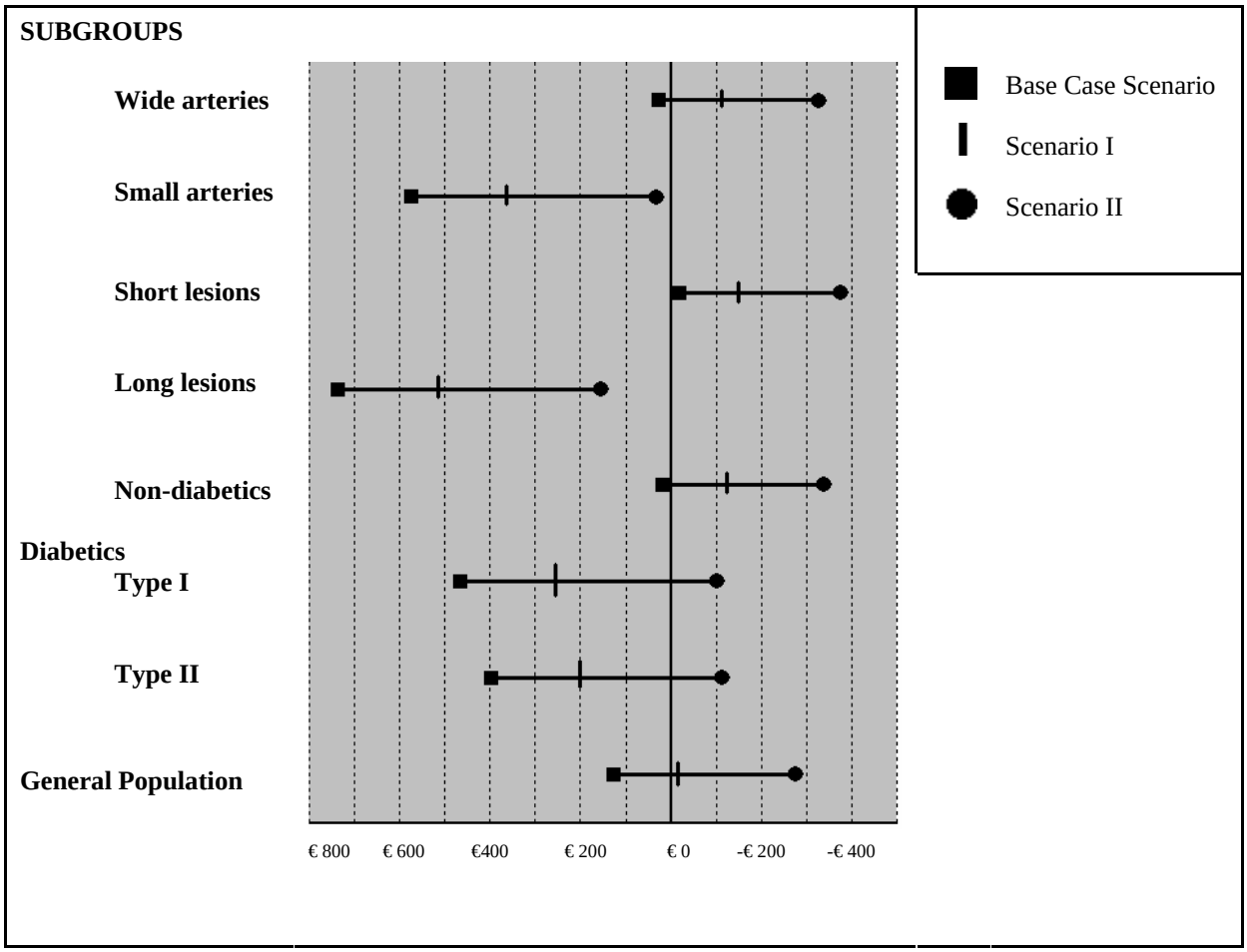
Variations in the device effectiveness

In the first sensitivity analysis the impact of a variation in the effectiveness of the stent devices was measured. In this study we only took into account the TAXUS and Cypher stents, there are however many other stents on the market, like for example the MULTILINK VISION^{TM}, which is the most effective bare metal stent (according to many physicians). The difference in effectiveness between BMS and DES may therefore be smaller in reality than in this study.[13] Therefore two sensitivity analyses were performed in which the effectiveness of the bare metal stent devices was fixed as being respectively 10 % (Scenario I) and 25 % (Scenario II) higher than in the base case analysis. Outcomes are presented in figure 3.

Table 4: Overview of the sensitivity analyses

Scenario I: effectiveness of BMS is 10 % higher than base case
Scenario II: effectiveness of BMS is 25 % higher than base case
Scenario III: extra cost of DES compared to BMS is € 1162 instead of € 1000
Scenario IV: extra cost of DES compared to BMS is € 650 instead of € 1000
Scenario V: cost of a patient with in-stent restenosis is 5 % higher than base case

Figure 3: Net cost savings for the use of Taxus DES under the assumptions of Scenario I & II



As would be expected, the net cost savings generated diminish as the effectiveness difference between BMS and DES declines. When increasing the effectiveness of the BMS by10%, there are still small positive net cost savings for the high-risk subgroups. Under the assumption of Scenario I the use of TAXUS DES by low-risk patient groups will result in an extra cost. The net cost savings for the general population are small for both the TAXUS stent device and the Cypher stent device.

If the BMS is considered to be far more effective than in the base case analysis (25% less restenoses) the use of TAXUS DES only seems to be cost saving for the risk groups 'long lesions' and 'small arteries'. The use of TAXUS DES for the population as a whole, for the

low risk patient groups and even for the risk group 'diabetics' is not cost saving under the assumptions of Scenario II. The use of Cypher DES under the assumptions of Scenario II results in negative cost savings for all possible patient groups.

Variations in the price of the coronary stent systems

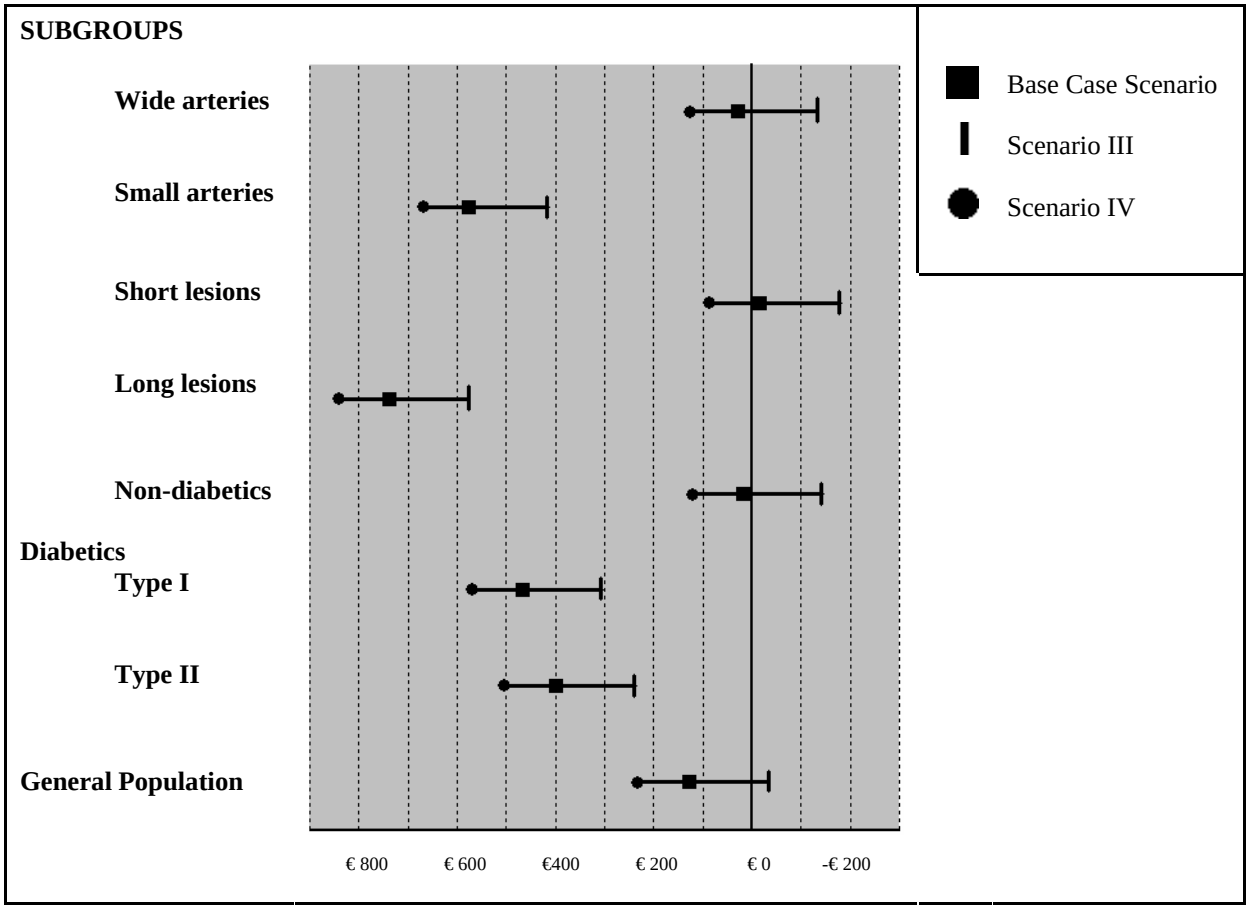
In the base case scenario the extra cost for DES of € 1000 set by the HIS was used. At the time of performing this study the purchase price of DES for the UZA was however € 1,616 compared with a purchase price of € 786 for BMS. Taking into account that the clinical trials report that on average 1.4 stents are used per stenting procedure this results in an extra cost of 1.4 * (1,616 – 786) = € 1,162 per intervention. Using these extra costs for the use of DES the expected cost savings were recalculated. The calculated net cost savings are presented in figure 4. (Scenario III)

As the market of DES is a relatively young market with new expected market entries, analysts predict that the price will decline.[13, 14, 15] Using the estimations of analysts and the price evolution in the last two years, we are convinced that a price difference between DES and BMS of € 650 could be expected in the short term. This purchase price difference was used to run the fourth scenario (Scenario IV). (Figure 4)

Using an extra cost of € 1,162 for the primary intervention with DES (the extra cost the UZA effectively pays) (instead of the HIS-tariff), the use of TAXUS DES is only cost saving for the high-risk patient groups. Under the assumptions of Scenario III, the use of TAXUS DES for low-risk patient groups is not cost saving. Considering the Cypher stent device, the use of DES is cost saving for diabetics and generates an extra cost for non-diabetics.

All of the calculated net cost savings are positive under Scenario IV, which means that if the actual trend of the reduction of the purchase price of DES continues, the use of DES will become cost saving for both high- and low-risk patients groups.

Figure 4: Net cost savings for the use of Taxus DES under the assumptions of Scenario III & IV

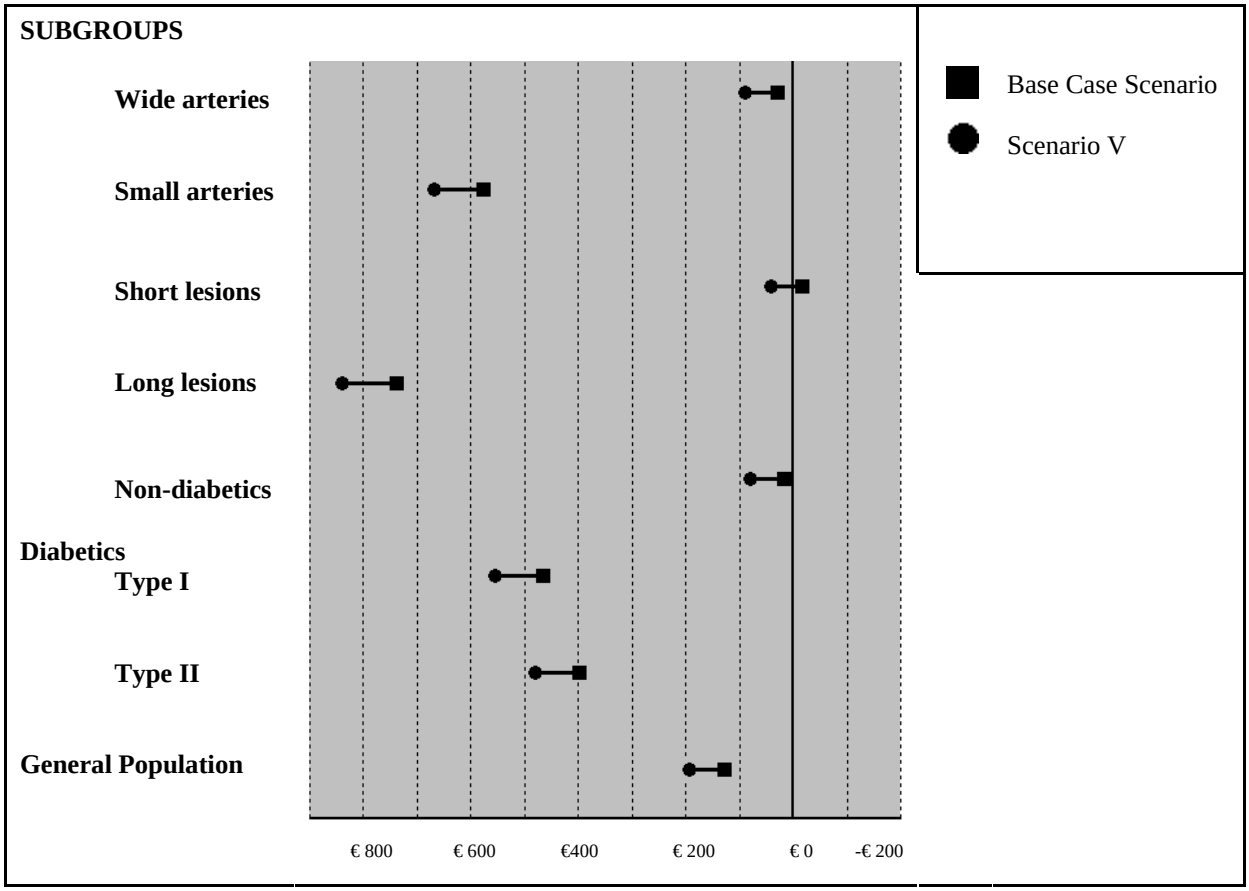


Variations in the cost of revascularization

An important parameter in the cost study has been the cost per revascularization procedure. The major point of uncertainty concerning this parameter is that the calculated revascularization cost only includes costs made in the UZA itself. Costs for supplemental medication and additional follow-up outside the UZA have not been included. Therefore the calculated cost of treatment of in-stent restenosis is an underestimation of the real cost. In Scenario V the cost generated by a patient with in-stent restenosis was fixed 5 % higher than in the base case analysis. Under the assumptions of Scenario V the use of DES becomes cost-

saving for nearly all types of patients. A net cost was found only for patients with short lesions initially receiving a TAXUS stent device. (Figure 5)

Figure 5: Net cost savings for the use of Taxus DES under the assumptions of Scenario V



LIMITATIONS

LIMITATIONS OF THE EFFECTIVENESS STUDY

It is important to point out that the results of the effectiveness studies must be interpreted with caution as none of the studies used can be considered as independent. All the clinical trials have been performed and reported by the stent manufacturers themselves. Moreover, all trials reported relatively limited data concerning the subgroups, and the follow-up period of the patients is limited to one year after the stent implantation. Finally, the patient population of the studies used is fully North-American: regarding the different cardiovascular profile of North-Americans and Europeans, this makes the effectiveness data not 100% applicable in a Belgian context.[16]

LIMITATIONS OF THE COST STUDY

The main limitation of the cost study is that the available data did not allow us to split the population into diabetics and non-diabetics. This could have been important as diabetics do not only have a significant higher risk of restenosis; diabetes is also expected to have an impact on the revascularization costs.

Furthermore the revascularization cost estimation only includes costs made in the UZA. Other costs such as diagnostic costs, costs for ambulatory follow-up and ambulatory drugs provided out of the UZA have not been included. Therefore the estimated cost per revascularization is expected to be an underestimation of the real restenosis cost.

Finally, the nature of cardiovascular disease makes it difficult to determine whether the main reason for a new intervention was restenosis in the stented lesion itself. Especially in patients with an advanced state of cardiovascular disease, the treated in-stent restenosis was only one of the main reasons for a new intervention. Nevertheless it was decided not to exclude these patients as otherwise; only patients in relatively better physical condition would remain.

DISCUSSION

This is the first study to compare costs of DES and BMS in Belgium. The main result of this study is the finding that in the base case scenario the use of DES is cost saving for the general population. Results of the sensitivity analyses however prove the sensitiveness of these results to the uncertainties in the study, which precludes a final conclusion concerning the use of DES for the entire population. For patients with a high restenosis risk however, the use of DES seems to be cost saving under almost all scenarios. This conclusion supports the actual HIS-policy to finance the use of DES for diabetic patients but also raises the question whether the HIS should consider financing the use of DES for other high-risk groups such as patients with long lesions and small arteries. Although this study is thus too limited to prove or reject the proposition that the use of DES is cost saving for all types of patients, there are strong indications that this could become the case in the long run. A price decrease of DES, expected by market researchers, could make the use of DES cost saving for the majority of the population, if not for everyone.

It is important to stress that when interpreting this study one should always keep in mind that the focus was only on medical cost issues. Other important aspects such as an increase in life expectancy, a possible improved quality of life and the avoidance of social and economic costs were not considered or valued. Net cost savings of €0 when comparing a DES with a BMS stent device means from a medical cost viewpoint that both options are equal. BMS however will have higher rates of angina and repeat revascularization interventions, and this definitely has a disutility value. Yock et al[17] report one month of good cardiac health as equal to 0.08 Qalys, and the patient utility of one month with return of symptoms equal to 0.07 Qalys. Taking into consideration a possible increase in life expectancy, an improved quality of life and the avoidance of social and economical costs due to the use of a more effective stent device, DES stent devices will turn out to be the better option. Even in the case of additional costs for the use of DES for some types of patients, health care decision makers should address the question whether the extra (long-term) medical cost for the use of these DES can be justified from a social viewpoint or not. In a broader perspective than medical costs, the use of DES is thus expected to turn out much more beneficial.

The use of DES as an alternative to BMS is an area of current debate. A number of studies in different countries have been devoted to it. The majority of those studies find that the use of DES for the entire population is not cost saving compared to the use of

BMS[12,18,19,20,21,22,23,24,25,26,27]. Through a significant lower rate of revascularizations there is a substantial reduction in follow-up costs, but this cost reduction does not fully offset the high initial procedure costs of DES. The additional costs per patient vary; from as low as € 166[25] to Can$ 2,500[19]. The extra cost of a DES over a BMS is one of the driving forces in the cost differences.

Studies calculating costs per QALY, find costs which are slightly above what is generally accepted as cost-effective; e.g. costs per QALY of respectively more than € 50,000[22], Aus$ 47,000-76,000[19], $ 27,540[12] and Can$ 58,700[20].

The studies that investigate the impact of the use of DES in specific high-risk subgroups all have corresponding results[12,19,220,22,23,24,26,27]. It is found that for these subgroups the use of DES is cost saving. The definition of subgroups differs for the different studies but usually they contain diabetics, patients with small vessels, patients with long lesions and elderly patients.

Almost all of these studies mention that the results are very sensitive to parameter input, especially to the price of DES. If the price of DES would fall, general use of DES could become cost-effective in the near future. Two studies calculate the break-even purchase cost of DES; Brophy et al[27] find a break even cost of Can$ 1,161 and Tarricone et al[18] find a purchase cost of € 1,371.

Under current conditions the literature concludes that general substitution of BMS by DES is not justified and only selected use of DES by patients in high-risk subgroups should be recommended. This conclusion corresponds with the results of the Belgian study, although in general our study results are more favorable to DES than those of the other countries.

CONCLUSION

We can concur in the existing literature and conclude that the use of drug-eluting stents instead of bare metal stents during a PCI is cost saving for high risk patients such as diabetics, patients with long lesions and patients with small vessels. Our study results suggest that even if the use of drug-eluting stents is not yet cost saving for medium and low risk patients, it could be worthwhile considering its use in these patients as well in the near future, when the device price diminishes.

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Any remaining errors are the authors' responsibility.

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Appendix 1: Cost calculations

As stated, the average cost of a revascularization procedure caused by in-stent restenosis at the UZA has been calculated:

CABG: € 18,972

PCI: € 6,803

To continue the analysis not the average cost per revascularization procedure but the average cost per restenosis patient is needed. Since clinical trials only report the number of patients with one or more revascularization procedure(s), the actual number of revascularization procedures is not known and this makes it impossible to calculate the average cost per patient accurately.

The information we have is stated in table 1:

Table 1: effectiveness of the Cypher and Taxus stents

	CYPHER		**TAXUS**	
	DES	BMS	DES	BMS
GENERAL POPULATION				
TLR	4.9 %	20 %	4.4 %	15.1 %
TLR-PCI	4.3 %	19.2 %	3.7 %	12.2 %
TLR-CABG	0.9 %	1.7 %	0.8 %	3.7 %

It is clear that TLR-PCI and TLR-CABG do not add up to TLR. This is because some patients with restenosis undergo a PCI procedure and restenosis immediately occurs again. These patients are then treated with a CABG-procedure. That is why some patients occur twice in the dataset. Despite this irregularity these are the best effectiveness data we could retrieve so we use them in our further analysis.

It is obvious from table 1 that the prevalence of both clinical endpoints (CABG and PCI) differs for the 4 stent systems. That is why an average cost per patient is calculated for every stent seperately.

- Cypher DES:
$$\left[\frac{4.3}{4.9} * 6802.69\right] + \left[\frac{0.9}{4.9} * 18972.09\right] = 9454.38$$

- Cypher BMS
$$\left[\frac{19.2}{20} * 6802.69\right] + \left[\frac{1.7}{20} * 18972.09\right] = 8143.21$$

- Taxus DES
$$\left[\frac{3.7}{4.4} * 6802.69\right] + \left[\frac{0.8}{4.4} * 18972.09\right] = 9169.91$$

- Taxus BMS
$$\left[\frac{12.2}{15.1} * 6802.69\right] + \left[\frac{3.7}{15.1} * 18972.09\right] = 10145.00$$

Table 2: Average restenosis costs per patient per stent

	Cypher		**TAXUS**[7]	
	DES	BMS	DES	BMS
Average Cost	**€ 9,454.38**	**€ 8,143.21**	**€ 9,169.91**	**€ 10,145.00**

Now we can calculate the net cost (savings) of the use of DES compared to BMS.

<u>The net cost savings of the use of Cypher DES:</u>

Average expected restenosis cost of patients treated with Cypher BMS:
% of patients with restenosis * average restenosis cost per patient =
0.20 * 8,143.21 = **1,628.64 per patient**

Average expected restenosis cost of patients treated with Cypher DES:
% of patients with restenosis * average restenosis cost per patient =
0.049 * 9,454.38 = **463.27 per patient**

cost difference use Cypher DES versus Cypher BMS:
1,628.64 – 463.27 = 1,165.37

the incremental cost of DES is €1000

net cost savings of use Cypher DES:
1,165.37 – 1000 = **165.37**

<u>The net cost savings of the use of Taxus DES:</u>

Average expected restenosis cost of patients treated with Taxus BMS:
% of patients with restenosis * average restenosis cost per patient =

[7] The average treatment cost of the TAXUS BMS is higher than that of the TAXUS DES. This is counterintuitive and not the case for the Cypher stents. This difference can be explained by the fact that, compared to the patients in the Cypher BMS group, much more patients in the TAXUS BMS patient group had to undergo CABG (3.7% vs 1.7% respectively). Since CABG is much more expensive than PCI, the cost of the TAXUS BMS exceeds that of the TAXUS DES. Whether the high number of CABGs in the TAXUS group is caused by the use of the TAXUS stent or is merely due to coincidence was not investigated.

0.151 * 10,145 = **1,531.90 per patient**

Average expected restenosis cost of patients treated with Taxus DES:
% of patients with restenosis * average restenosis cost per patient =
0.044 * 9,169.91 = **403.48 per patient**

cost difference use Taxus DES versus Taxus BMS:
1,531.90 – 403.48 = 1,128.48

the incremental cost of DES is €1000

net cost savings of use Taxus DES:
1,128.48 – 1000 = **128.48**

For the subgroups we have no data on the number of patients that undergo PCI and/or CABG. We decided to use the same percentages as for the general population and consequently use the same cost for DES and BMS (table 2).
We have summarized the calculations of the net cost savings of the use of DES in table 3 for the Cypher stent and table 4 for the Taxus stent.

Table 3: calculation of the net cost savings of the use of Cypher DES for subgroups

SUBGROUP	**Diabetics**	**Non-diabetics**	**Long lesions**	**Short lesions**	**Small arteries**	**Wide arteries**
BMS						
Cost TLR	€ 8,143.21	€ 8,143.21	€ 8,143.21	€ 8,143.21	€ 8,143.21	€ 8,143.21
Restenosis probability	26.40%	17.60%	21.90%	18.60%	22.30%	18.10%
Average expected restenosis cost	€ 2,149.81	€ 1,433.20	€ 1,783.36	€ 1,514.64	€ 1,815.94	€ 1,473.92
DES						
Cost TLR	€ 9,454.38	€ 9,454.38	€ 9,454.38	€ 9,454.38	€ 9,454.38	€ 9,454.38
Restenosis probability	8.40%	3.70%	6.00%	4.00%	6.60%	3.10%
Average expected restenosis cost	€ 794.17	€ 349.81	€ 567.26	€ 378.18	€ 623.99	€ 293.09
Cost difference DES - BMS	€ 1,355.64	€ 1,083.39	€ 1,216.10	€ 1,136.46	€ 1,191.95	€ 1,180.83
Extra cost DES	€ 1,000.00	€ 1,000.00	€ 1,000.00	€ 1,000.00	€ 1,000.00	€ 1,000.00
Net cost savings of use DES	**€ 355.64**	**€ 83.39**	**€ 216.10**	**€ 136.46**	**€ 191.95**	**€ 180.83**

Table 4: calculation of the net cost savings of the use of Taxus DES for subgroups

SUBGROUP	**Diabetics**		**Non-diabetics**	**Long lesions**	**Short lesions**	**Small arteries**	**Wide arteries**
	Type I	**Type II**					
BMS							
Cost TLR	€ 10,145.00	€ 10,145.00	€ 10,145.00	€ 10,145.00	€ 10,145.00	€ 10,145.00	€ 10,145.00
Restenosis probability	19.40 %	21.60 %	13.20 %	22.10 %	13.40 %	20.60 %	13.30 %
Average expected restenosis cost	€ 1,968.13	€ 2,191.32	€ ,339.14	€ 2,242.05	€ 1,359.43	€ 2,089.87	€ 1,349.29
DES							
Cost TLR	€ 9,169.91	€ 9,169.91	€ 9,169.91	€ 9,169.91	€ 9,169.91	€ 9,169.91	€ 9,169.91
Restenosis probability	6.20 %	7.90 %	3.50 %	5.50 %	4.10 %	5.60 %	3.50 %
Average expected restenosis cost	€ 568.53	€ 724.42	€ 320.95	€ 504.35	€ 375.98	€ 513.52	€ 320.95
Cost difference DES - BMS	€ 1,399.60	€ 1,466.90	€ 1,018.19	€ 1,737.70	€ 983.45	€ 1,576.35	€ 1,028.34
Extra cost DES	€ 1,000	€ 1,000	€ 1,000	€ 1,000	€ 1,000	€ 1,000	€ 1,000
Net cost savings of use DES	**€ 399.60**	**€ 466.90**	**€ 18.19**	**€ 737.70**	**- € 16.55**	**€ 576.35**	**€ 28.34**

In table 5 the net cost savings of DES are summarized for both types of stents.

Table 5: Estimated net cost savings of the use of DES instead of BMS.

	Cypher DES	**TAXUS DES**
GENERAL POPULATION	€ 165.37	€ 128.48
SUBGROUPS		
Diabetics	€ 355.64	
Type I		€ 399.60
Type II		€ 466.90
Non-diabetics	€ 83.39	€ 18.19
Long lesions	€ 216.10	€ 737.70
Short lesions	€ 136.46	- € 16.55
Small coronary arteries	€ 191.95	€ 576.35
Wide coronary arteries	€ 180.83	€ 28.34